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PALLADIUM CATALYSED C-8 ALLYLATION AND VINYLATION OF ADENOSINE, 2'-DEOXYADENOSINE AND 2',3'-DIDEOXYADENOSINE NUCLEOSIDES

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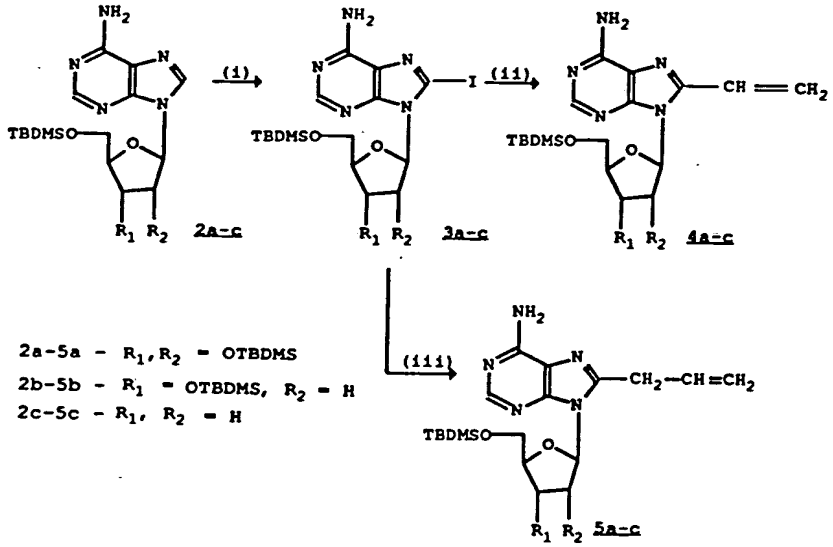
Abstract:
Using a coupling reaction between 8-iodo derivatives of O-TBDMS protected adenosine, 2'-deoxyadenosine, 2',3'-dideoxyadenosine and either vinyltributyltin or allyltributyltin with $Pd(PPh_3)_4$ catalysis, the corresponding 8-substituted nucleosides were obtained in excellent yields.

Modified 2-'deoxy and 2',3'-dideoxynucleosides are of interest due to their remarkable biological activity, particularly within the context of anti-viral therapeutic agents[1-3]. Such modified nucleoside analogues can be used for example, in the design of 'antisense' polynucleotides[4,5],sequence specific DNA cleaving agents[6]and in sequencing DNA[7,8].

Several methods have been reported for the functionalization[9] of the C-8 position of purine nucleosides. Direct bromination (in a pH controlled buffer) at the C-8 position[10a,b] and subsequent nucleophilic displacement was one of the earliest approaches. Synthetically more satisfactory is the lithiation of the C-8 position of hydroxy protected purine nucleoside with lithium diisopropylamide[11] or n-butyl lithium[12] and reaction with suitable electrophiles. Palladium catalysed coupling of alkynes[13] with 8- bromo purine nucleosides has also been reported. However there exists less precedence in the literature for C-8 functionalization of 2'-deoxy[10b,14] and 2',3'-dideoxy purine nucleosides.

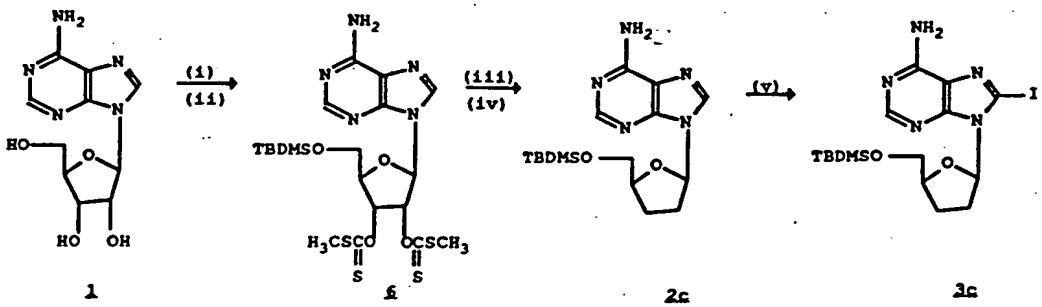
In connection with our interest in functionalized 2'-deoxy and 2',3'-dideoxynucleosides we required C-8 allyl and vinyl analogues as substrates for further transformation. In this communication we report the allylation and vinylation of the C-8 position of t-butyldimethylsilyloxy derivatives of adenosine, 2'-deoxyadenosine and 2',3'-dideoxyadenosine by subjecting the 8-iodo derivatives to Pd catalysed cross coupling with allyl and vinyltributyltin[15](Table 1).

Iodination of the C-8 position using a procedure similar to Miyasaka's for 8-iodo cordycepin[16a], namely lithiation of the C-8 position of hydroxy protected (with TBDMSCl) nucleoside with LDA at -78°c in THF and quenching with iodine, yielded 3a-c (Scheme 1). The iodination proceeded with moderate to satisfactory yields[16b] [3a-(72%), 3b-(80%), 3c-(65%)]. Since protection of the OH groups with TBDMSCl made the nucleosides less polar and hence easier to handle and purify, the protecting groups were retained for the Pd catalysed reactions.



i) LDA, -78 °c, THF, I_2 (ii) vinyltributyltin, $Pd(PPh_3)_4$, DMF, r.t. to 95 °c
(iii) allyltributyltin, $Pd(PPh_3)_4$·, HMPA, r.t. to 145 °c

Scheme 1



i) TBDMSCl, imidazole, DMF (ii) NaOH, CS_2, CH_3I, DMSO (iii) Bu_3SnH, AIBN, toluene, refl.
(iv) H_2, Pd/C, CH_3OH (v) LDA, -78 °c, THF, I_2

Scheme 2

Heating 8-iodo adenosine analogues (3a-c) from r.t. to 90-95°c. with vinyltributyltin and 5 mol% $Pd(PPh_3)_4$ in DMF gave the C-8 vinyl nucleosides (4a-c) in high yields after chromatography[17]. Under the same conditions allylation did not take place satisfactorily, yielding a mixture of the desired C-8 allyl nucleoside derivative and C-8 deiodinated nucleoside derivative .This was not totally unexpected because it has been reported that aryl iodides are poor substrates for Pd catalysed allylation with allyltributyltin[18]. Success was achieved using HMPA as the solvent and increasing the temperature to 145°c. Under these conditions the reaction proceeded cleanly, yielding very little of the deiodinated starting material.

Table-1

Synthesis[17] of 8-allyl and vinyl t-butyldimethylsilyloxy derivatives of adenosine

Starting Material[b]	Product[b]	Yield %[a]	M.P.(°c)
3a	4a	92	179-180
3b	4b	89	112-114
3c	4c	90	148-150
3a	5a	81	138-140
3b	5b	89	132-133
3c	5c	75	84-85

a) Isolated yield after chromatography
b) Characterized by IR, ^1H and ^{13}C NMR and mass spectra.

5'-OTBDMS 2',3'-dideoxyadenosine (2c)was prepared following the procedure by Chu et al.[19](Scheme 2).These workers were unable to reduce the 5'-OTBDMS 2',3'-didehydro-2',3'-dideoxy adenosine to the corresponding 5'-OTBDMS 2',3'-dideoxy derivative directly with H_2/ Pd without prior deprotection of the 5'-OTBDMS group[20]. We found that this could be done directly or after pretreatment with Raney Ni[21].Iodination and coupling of the dideoxy derivative proceeded satisfactorily as well.

In summary we have synthesized C-8 allyl and vinyl derivatives of 2',3',5'-tri OTBDMS adenosine, 3',5'-di OTBDMS 2'-deoxyadenosine and 5'-OTBDMS 2',3'-dideoxyadenosine. This approach should be general for other purine nucleosides as well.

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CH ═══ CH_2

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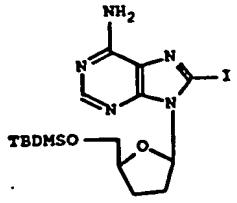
r.t. to 95 °c



3c

IBN,toluene,refl.

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b) 8-iodo t-butyldimethylsilyloxy nucleosides (3a-c) were purified through flash chromatography. While 3a was a crystalline solid (m.p.171-172.5°c), 3b and 3c were obtained as foams. They were directly used in the Pd catalysed reactions, without further recrystallization.
17) In a typical vinylation reaction, to a stirred mixture of 8-iodo t-butyldimethylsilyloxy nucleoside (1eq.) and $Pd(PPh_3)_4$ (5 mol%) in DMF (under Ar), vinyltributyltin (5eq.) was added. The mixture was heated from r.t. to 90-95°c for 30-45 min. TLC showed near quantitative conversion. Workup was done by adding aq. sat. NH_4Cl, extracting with EtOAc, drying with anhyd. Na_2SO_4 and evaporating to dryness in vacuo. The crude mixture thus obtained was flash chromatographed on silicagel to yield the pure product, which crystallized either directly or upon cooling to 0°c in hexanes. For allylation a similar procedure and workup was used, except for using HMPA as the solvent and heating from r.t. to 145°c for 30-45 min. TLC again showed high conversion. Though the products 5a and 5b readily crystallized in hexanes at 0°c, crystallization of 5c was not completely satisfactory, tending to remain as a semi-solid or as an oil .
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